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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/081,922
Filing Date: February 21, 2002
Appellant(s): LISZIEWICZ ET AL.

Valerie Looper
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12-16-08 appealing from the Office action mailed 4-16-08.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows:

Claim 23 was not rejected regarding the phrase "without the use of a needle." Support for the phrase "without the use of a needle" was found in the abstract as stated in the office action sent 4-16-08;

The new matter rejection regarding "DNA and a sugar" has been withdrawn.

The obviousness-type double patenting rejection has been withdrawn because 08/803,484 has been abandoned.

I. Claim 30 stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the phrase "method of claim 28, wherein the complex comprises a 5:1 ratio of mannosylated polyethylenimine nitrogen per DNA phosphate" remains unclear.

II. Claims 23-26, 28, 30-32, 35, 40, 41, 43 and 44 stand rejected under 35 U.S.C. 102(e) as being anticipated by Behr (US Patent 6,013,240, Jan. 11, 2000; 102(e) date=2-28-97) as supported by Liu (Vaccine, 2002, Vol. 20, pg 42-48), Mittal (J. General Virol., Jan. 1996, Vol. 77, pg 1-9, abstract only) and Kuby (ed., Immunology, 1992, W.H. Freeman and Company, Chapter 1, "Acquired Immunity," pg 8-9).

III. Claims 23-26, 28, 30-32, 35, 40, 41, 43 and 44 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Behr (US Patent 6,013,240, Jan. 11, 2000) as supported by Liu (Vaccine, 2002, Vol. 20, pg 42-48), Mittal (J. General Virol., Jan. 1996, Vol. 77, pg 1-9, abstract only) and Kuby (ed., Immunology, 1992, W.H. Freeman and Company, Chapter 1, "Acquired Immunity," pg 8-9) and in view of Holler (US Patent 5,908,923).

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Liu (Vaccine, 2002, Vol. 20, pg 42-48)

Mittal (J. General Virol. Jan. 1996, Vol. 77, pg 1-9, abstract only)

Kuby (ed., Immunology, 1992, W.H. Freeman and Company, Chapter 1, "Acquired Immunity," pg 8-9)

6013240	Behr	1-2000
5908923	Holler	6-1999

(9) Grounds of Rejection

Double Patenting

The rejection of claims 23-26, 28, 30-33, 35 and 40-44 as being provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 58-71 of copending Application No. 08/803484 in view of the disclosure of '484 has been withdrawn because '484 has been abandoned.

New Matter

Contrary to the Appeal Brief, claim 23 was not rejected under new matter regarding the phrase "without the use of a needle." Support for "without the use of a needle" in claim 23 as amended on 1-7-08 was found in the last line of the abstract as stated on pg 3 of the office action sent 4-16-08.

The rejection of claims 23-26, 28, 30-33, 35 and 40-44 under 35 U.S.C. 112, first paragraph, new matter regarding a gene delivery complex comprising "DNA and a sugar, or polyethylenimine, or polyethylenimine derivatives" in claim 23 has been withdrawn. Support can be found on pg 24, lines 34-35.

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

Indefiniteness

I. Claim 30 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the phrase "method of claim 28, wherein the complex comprises a 5:1 ratio of mannosylated polyethylenimine nitrogen per DNA phosphate" remains unclear. It is unclear what applicants consider a mannosylated polyethylenimine nitrogen and how such nitrogens are distinguished from polyethylenimine nitrogen. Claim 30 does not clearly first limit the complex to having mannosylated polyethylenimine; therefore, limiting the complex to having a 5:1 ratio of mannosylated PEI nitrogen per DNA phosphate without first limiting the complex to one having mannosylated PEI does not make sense because the complex can made with sugar (see claim 23). Furthermore, the limitation in claim 30 does not further limit the "mannosylated polyethylenimine" of claim 26. Overall, the phrase is unclear.

Claim Rejections - 35 USC § 102

II. Claims 23-26, 28, 30-32, 35, 40, 41, 43 and 44 stand rejected under 35 U.S.C. 102(e) as being anticipated by Behr (US Patent 6,013,240, Jan. 11, 2000; 102(e) date=2-28-97) as supported by Liu (Vaccine, 2002, Vol. 20, pg 42-48), Mittal (J. General Virol., Jan. 1996, Vol. 77, pg 1-9, abstract only) and Kuby (ed., Immunology, 1992, W.H. Freeman and Company, Chapter 1, "Acquired Immunity," pg 8-9) for reasons of record.

Parent application 60/058,933 did not describe complexing DNA with a compound selected from the group consisting of sugars, PEI or PEI derivatives (claim

23). Therefore, claim 23 does not get priority back to parent application 60/058,933 (filed 9-15-97). Parent application 09/153,198 (filed 9-15-98) described complexing DNA with PEI-mannose in a 5-10% glucose solution on pg 26, lines 1-9. Therefore, claim 23 has priority to 9-15-98.

Behr taught a complex comprising i) PEI, and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter suspended in 5% glucose (col. 12, lines 53-57). Behr taught administering any complex of the invention to the skin or mucosa of an animal (claim 33, col. 6, lines 1-19). More specifically, Behr taught topical, cutaneous, oral, rectal, vaginal, parenteral and intranasal application (col. 6, lines 1-4), which is equivalent to applying the gene delivery complex to the skin or mucosa without the use of a needle as claimed.

The steps described by Behr encompass applying DNA encoding HIV by a number of means that do not require a needle; there is no reason to doubt the complex described by Behr would inherently transfect APCs because the steps are identical to those described by applicants. For example, applying a gene delivery complex topically as described by Behr inherently results in transfecting APCs as supported by Liu (see entire article). Liu has been used to solely to support the fact that transfection of APCs would inherently and naturally flow from applying a gene delivery complex topically as described by Behr.

Luciferase is an immunogenic protein because it is foreign to mammals and induces an immune response in mammals. Mittal taught luciferase induces antibodies in rats (second to last sentence of the abstract). Luciferase must be immunogenic as

claimed in any animal other than fireflies because it is a protein isolated from fireflies and because proteins isolated from one animal and introduced into another animal are recognized as foreign by the immune system and cause an immune response (Kuby, pg 8-9). In the alternative, Behr taught the DNA could encode an HIV peptide (col. 3, lines 57-67).

Claims 25, 26 and 43 are included because they are not limited to a compound that is mannosylated PEI or PEI "from a PEI 22 kDA;" claims 25, 26 and 43 encompass non-sugar-modified PEI solubilized in glucose as in parent claim 24.

Claims 28 and 30 are included because Behr taught that between 5-20 equivalents of PEI amines are used relative to one DNA phosphate (col. 8, lines 15-19). The instant specification teaches that the ratio of 5:1 cause the complex to be electrostatically neutral (¶ bridging pg 21-22).

Claim 33 has been excluded because 5% is not "8%" as newly amended.

Claims 35 and 41 are included because administering the complex to the skin/mucosa as taught by Behr inherently would activate APCs by toxin activation. Cells would start expressing luciferase and this firefly "toxin" would be recognized as foreign by the animal, thereby activating APCs, including Langerhans cells.

Claim Rejections - 35 USC § 103

III. Claims 23-26, 28, 30-32, 35, 40, 41, 43 and 44 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Behr (US Patent 6,013,240, Jan. 11, 2000) as supported by Liu (Vaccine, 2002, Vol. 20, pg 42-48), Mittal (J. General Virol., Jan. 1996, Vol. 77, pg 1-9, abstract only) and Kuby (ed., Immunology, 1992, W.H. Freeman

and Company, Chapter 1, "Acquired Immunity," pg 8-9) and in view of Holler (US Patent 5,908,923).

This obviousness rejection is an artifact from canceled claim 39; it applies to the remaining claims because it more closely reflects the DNA encoding HIV-1/LWint-used by applicants (pg 18, Example 1, lines 31-32).

Parent application 60/058,933 (9-15-97) did not describe complexing DNA with sugars, PEI or PEI derivatives (claim 23). Parent application 09/153,198 (9-15-98) described complexing DNA with PEI-mannose in a 5-10% glucose solution on pg 26, lines 1-9; therefore, claim 23 has priority to 09/153,198 (9-15-98).

Behr taught a complex comprising i) PEI, and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter suspended in 5% glucose (col. 12, lines 53-57). Behr taught administering any complex of the invention to the skin or mucosa of an animal (claim 33, col. 6, lines 1-19). More specifically, Behr taught topical, cutaneous, oral, rectal, vaginal, parenteral and intranasal application (col. 6, lines 1-4), which is equivalent to applying the gene delivery complex to the skin or mucosa without the use of a needle as claimed.

The steps described by Behr encompass applying the DNA complex by a number of means that do not require a needle; there is no reason to doubt the complex described by Behr would inherently transfect APCs because the steps are identical to those described by applicants. For example, applying a gene delivery complex topically as described by Behr inherently results in transfecting APCs as supported by Liu (see entire article). Case law established that reliance upon inherency in an obviousness

rejection (103) instead of an anticipation rejection (102) is proper. In re Skoner, et al. 186 USPQ 80 (CCPA).

Luciferase is an immunogenic protein because it is foreign to mammals and induces an immune response in mammals. Mittal taught luciferase induces antibodies in rats (second to last sentence of the abstract). Luciferase must be immunogenic as claimed in any animal other than fireflies because it is a protein isolated from fireflies and because proteins isolated from one animal and introduced into another animal are recognized as foreign by the immune system and cause an immune response (Kuby, pg 8-9). In the alternative, Behr taught the DNA could encode an HIV peptide (col. 3, lines 57-67).

Claims 25, 26 and 43 are included because they are not limited to a compound that is mannosylated PEI or PEI "from a PEI 22 kDA;" claims 25, 26 and 43 encompass non-sugar-modified PEI solubilized in glucose as in parent claim 24.

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Claim 33 has been excluded because 5% is not "8%" as claimed.

Claims 35 and 41 are included because administering the complex to the skin/mucosa as taught by Behr inherently would activate APCs by toxin activation. Cells would start expressing luciferase and this firefly "toxin" would be recognized as foreign by the animal, thereby activating APCs, including Langerhans cells.

Behr did not teach using a plasmid encoding a protein from a replication-defective, integrase-defective HIV (pg 18, Example 1, lines 31-32).

However, Holler taught a plasmid encoding a replication-defective HIV that was integrase defective for use in vivo (col. 4, lines 51-54).

Thus, it would have been obvious for one of ordinary skill in the art at the time the invention was made to apply a gene delivery complex comprising a plasmid encoding an HIV protein to the skin/mucosa of an animal as described by Behr, wherein the plasmid encoded a replication-defective, integrase-defective HIV as taught by Holler. One of ordinary skill in the art would have been motivated to make the HIV replication-defective and integrase-defective to prevent causing disease in the animal.

The combined teachings of Behr and Holler provide a reasonable expectation of successfully transfecting cells because Holler transfected CEM (a lymphoblastoid cell line) with integrase-defective HIV. Therefore, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of successfully transfecting APCs by applying the plasmid encoding the HIV taught by Holler to the skin or mucosa as taught by Behr.

(10) Response to Argument

New Matter

No new matter rejections remain standing.

I. **Indefiniteness**

Applicants indicate willingness to amend claim 26 changing its dependency to claim 24 and replace "derivative is" with –complex comprising DNA and-- (pg 29-30 of the Appeal Brief filed 12-16-08). Applicants' willingness is noted but inadequate to overcome the rejection. Applicants have not addressed the basis of the indefiniteness rejection. The metes and bounds of what applicants consider a mannosylated polyethylenimine nitrogen and how such nitrogens are distinguished from polyethylenimine nitrogen cannot be determined.

On pg 9 of the Appeal Brief filed 12-16-08, applicants state support for the phrase is found on pg 22, lines 9-16. Applicants' argument is not persuasive. Pg 22 teaches how to neutralize PEI with the DNA but does not clarify the metes and bounds of the claim.

II. **Anticipation**

Applicants argue Liu was not available as prior art (pg 30 of Appeal Brief filed 12-16-08); therefore, applicants argue Liu cannot be used as part of the rejection. Applicants' argument is not persuasive. Liu has not been used as prior art. Liu has been used solely to support the examiner's position that administering the complex to the skin or mucosa of an animal as described by Behr (claim 33, col. 6, lines 1-19) inherently transfects APCs as claimed. Post-filing art can support the Examiner's inherency argument.

Applicants argue the rejection should be withdrawn because the Examiner stated "transfection of antigen presenting cells 'may not occur' office action dated Sept. 22, 2004, at page 24, lines 2-3." Applicants' argument is not persuasive. Pg 24, lines 2-3,

of the office action states "The phrase 'transfecting antigen presenting cells' in the preamble does not bear patentable weight in considering the art because it may not occur." In the alternative, the examiner has provided evidence that even assuming the phrase does bear patentable weight, applying the complex to the skin as described by Behr inherently results in transfecting APCs as claimed as supported by Liu.

Applicants address Behr under the arguments to the obviousness rejection but not the arguments to the anticipation rejection. For completeness, applicants' arguments regarding Behr will be addressed as they relate to the anticipation rejection.

Applicants argue Behr is a general reference that lacks specific disclosure of inserting genes into APCs (pg 31 of Appeal Brief filed 12-16-08). Applicants' argument is not persuasive. Behr teaches all the steps and reagents required to apply a gene delivery complex to the skin and transfect APCs for reasons set forth in the rejection.

Applicants argue the specification teaches how to modify the teachings of Behr to apply it to a new class of cells by targeting a different receptor. Applicants point to Examples 6, 7, 8 and 10 of applicants' disclosure and argue they are different than the teachings of Behr, specifically Example 14 of Behr. Applicants' arguments are not persuasive. Behr is not limited to the teachings of Example 14. Furthermore, Behr taught that between 5-20 equivalents of PEI amines are used relative to one DNA phosphate (col. 8, lines 15-19), and the instant specification teaches that the ratio of 5:1 cause the complex to be electrostatically neutral (¶ bridging pg 21-22), which is equivalent to claims 28 and 30 and the teachings in Example 7. Therefore, the teachings in Behr overlap significantly with the teachings in applicants' disclosure.

Finally, and most importantly, the claims are not distinguished over the teachings of Behr (and supported by Liu, Mittal and Kuby). Applicants have failed to incorporate any element into the claims that distinguishes them over the teachings of Behr (supported by Liu, Mittal and Kuby). Accordingly, the rejection stands.

Applicants argue those of ordinary skill would not have had a reasonable expectation of success because multiple modification are required (pg 32 of Appeal Brief filed 12-16-08). Applicants' argument is not persuasive. Behr teaches all the steps claimed.

Applicants argue the Examiner's contention that "transfection with one type of cell is necessarily an indicator of success with another type of cell is contradicted by references cited in the text of the application" (pg 32 of Appeal Brief, last three lines). Applicants point to Pollard and Arthur references that demonstrate that dendritic cells have historically been more difficult to transfect than cancer cells. Applicants' arguments are not persuasive. Pollard shows PEI promotes transgene delivery to the nucleus of mammalian cells. Arthur compares gene transfer methods in human dendritic cells. The references have been reviewed, but it cannot be found where Pollard or Arthur show dendritic cells are more difficult to transfect than cancer cells. More importantly, it is unclear why such statements indicate the teachings of Behr are inadequate to transfect dendritic cells. Showing that transfection of dendritic cells is "difficult" is inadequate to overcome the rejection because transfection of dendritic cells was known to occur. In particular, Liu shows that applying a gene delivery complex to the skin as described by Behr inherently transfected APCs as claimed.

Applicants argue Mittal and Kuby do not fill the gaps in Behr because they do not relate to methods of in vivo gene delivery (pg 33 of Appeal Brief filed 12-16-08). Applicants' argument is not persuasive. Mittal and Kuby support the fact that luciferase is an immunogenic protein.

III. **Obviousness**

Applicants argue Behr is a general reference that lacks specific disclosure of inserting genes into APCs (pg 31 of Appeal Brief filed 12-16-08). Applicants' argument is not persuasive. Behr teaches all the steps and reagents required to apply a gene delivery complex to the skin and transfect APCs for reasons set forth in the rejection.

Applicants argue the specification teaches how to modify the teachings of Behr to apply it to a new class of cells by targeting a different receptor. Applicants point to Examples 6, 7, 8 and 10 of applicants' disclosure and argue they are different than the teachings of Behr, specifically Example 14 of Behr. Applicants' arguments are not persuasive. Behr is not limited to the teachings of Example 14. Furthermore, Behr taught that between 5-20 equivalents of PEI amines are used relative to one DNA phosphate (col. 8, lines 15-19), and the instant specification teaches that the ratio of 5:1 cause the complex to be electrostatically neutral (¶ bridging pg 21-22), which is equivalent to claims 28 and 30 and the teachings in Example 7. Therefore, the teachings in Behr overlap significantly with the teachings in applicants' disclosure. Finally, and most importantly, the claims are not distinguished over the combined teachings of Behr and Holler (and supported by Liu, Mittal and Kuby). Applicants have failed to incorporate any element into the claims that distinguishes them over the

combined teachings of Behr and Holler (supported by Liu, Mittal and Kuby). Accordingly, the rejection stands.

Applicants argue those of ordinary skill would not have had a reasonable expectation of success because multiple modification are required (pg 32 of Appeal Brief filed 12-16-08). Applicants' argument is not persuasive. The combined teachings of Behr and Holler teach all the steps claimed.

Applicants argue the Examiner's contention that "transfection with one type of cell is necessarily an indicator of success with another type of cell is contradicted by references cited in the text of the application" (pg 32 of Appeal Brief, last three lines). Applicants point to Pollard and Arthur references that demonstrate that dendritic cells have historically been more difficult to transfect than cancer cells. Applicants' arguments are not persuasive. Pollard shows PEI promotes transgene delivery to the nucleus of mammalian cells. Arthur compares gene transfer methods in human dendritic cells. The references have been reviewed but it cannot be found where Pollard or Arthur show dendritic cells are more difficult to transfect than cancer cells. More importantly, it is unclear why such statements indicate the teachings of Behr are inadequate to transfect dendritic cells. Showing that transfection of dendritic cells is "difficult" is inadequate to overcome the rejection because transfection of dendritic cells was known to occur. In particular, Liu shows that applying a gene delivery complex to the skin as described by Behr inherently transfected APCs as claimed.

Applicants argue Mittal, Kuby and Holler do not fill the gaps in Behr because they do not relate to methods of in vivo gene delivery (pg 33 of Appeal Brief filed 12-16-08).

Applicants reiterate and state Holler does not fill the gaps of Behr (pg 34 of Appeal Brief). Applicants' argument is not persuasive. Mittal and Kuby support the fact that luciferase is an immunogenic protein. Holler has been used as a secondary reference to support the fact that plasmids encoding a replication-defective HIV that were integrase defective for use in vivo were known in the art (col. 4, lines 51-54), which more closely reflect applicants invention (Example 1, pg 18, lines 31-32; canceled claim 39).

Applicants argue Liu was not available as prior art (paragraph bridging pg 33-34 of Appeal Brief filed 12-16-08); therefore, applicants argue Liu cannot be used as part of the rejection. Applicants' argument is not persuasive. Liu has not been used as prior art. Liu has been used to support the examiner's position that administering the complex to the skin or mucosa of an animal as described by Behr (claim 33, col. 6, lines 1-19) inherently transfects APCs as claimed. Liu need not be prior art to support the Examiner's inherency argument.

Double Patenting

No double patenting rejections remain standing.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Michael C. Wilson

/Michael C. Wilson/

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Peter Paras

/Peter Paras, Jr./

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